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# Early Visual Failure in Multiple Sclerosis due to a Primary Progressive Bilateral Optic Neuropathy

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**Introduction** Although involvement of the anterior visual system in multiple sclerosis is virtually ubiquitous, primary progressive visual failure commencing before or shortly after multiple sclerosis diagnosis is rare. Here, we describe a cohort with this rare phenotype that appears to affect a distinct demographic.

**Table 1. Applied diagnostic criteria PPON**

| | |
|---|---|
| **1)** | **Clinical** |
| | Progressive, painless visual loss for one year minimum (retrospectively or prospectively determined), without previous symptomatic optic neuritis; |
| | Onset of visual loss before, or no longer than 1 year later than, other relapsing or progressive multiple sclerosis associated symptoms. |
| **2)** | **MS Diagnosis** |
| | Fulfilling up-to-date panel consensus multiple sclerosis diagnostic criteria (Thompson et al., 2018a). |
| **3)** | **Neuro-ophthalmological evaluation** |
| | Clinical evidence for optic neuropathy; |
| | No family history of potentially hereditary optic neuropathy; |
| | Exclusion of other causes of optic neuropathy guided clinically. |

**Methods** This multi-centre international retrospective chart review, based at two neuro-ophthalmology clinics (Moorfields Eye Hospital, London, UK and Amsterdam University Medical Centre, Amsterdam, the Netherlands), described demographic, clinical and imaging features of patients with progressive visual failure presenting before or less than one year after multiple sclerosis onset. All cases fulfilled McDonald multiple sclerosis diagnostic criteria and had alternative causes for progressive optic neuropathy excluded (Table 1).

**Results** Sixteen multiple sclerosis patients (13 male; 81%) with early visual failure were identified between 1996 and 2019 (Table 2). The median age at onset of visual symptoms was 25 years (range 15 – 48). Eight patients (50%) were diagnosed with primary progressive multiple sclerosis, and out of eight cases initially diagnosed with relapsing-remitting multiple sclerosis, two developed secondary progressive disease during follow-up. Follow-up was available for a median of 6.5 years (range 1 – 23 years) since onset. Visual loss was bilateral in all cases. Eleven patients (69%) reported Uhthoff phenomenon. Five out of the eleven (45%) cases who received methylprednisolone treatment experienced improvement (although transient in four cases). Optical coherence tomography revealed severe inner retinal atrophy, with a median peripapillary retinal nerve fibre layer thicknesses of 62µm (range: 49 – 91) and a median macular ganglion cell and inner plexiform layer of 45µm (range: 35 – 72) (Table 3). Microcystic macular oedema (MMO) was present in 50% of macular scans (Figure 1).

**Table 2: Baseline characteristics**

| | |
|---|---|
| **N** | 16 |
| **Sex, m (%)** | 13 (81%) |
| **Age, median (range)** | 25 (15 – 48) |
| **RRMS / SPMS / PPMS** | 6 (37.5%) / 2 (12.5%) / 8 (50%) |
| **Uhthoff, yes (%)** | 11 (69%) |
| **Received IVMP (%)** | 11 (69%) |
| **Treatment effect, yes (%)** | 5 (45%) |

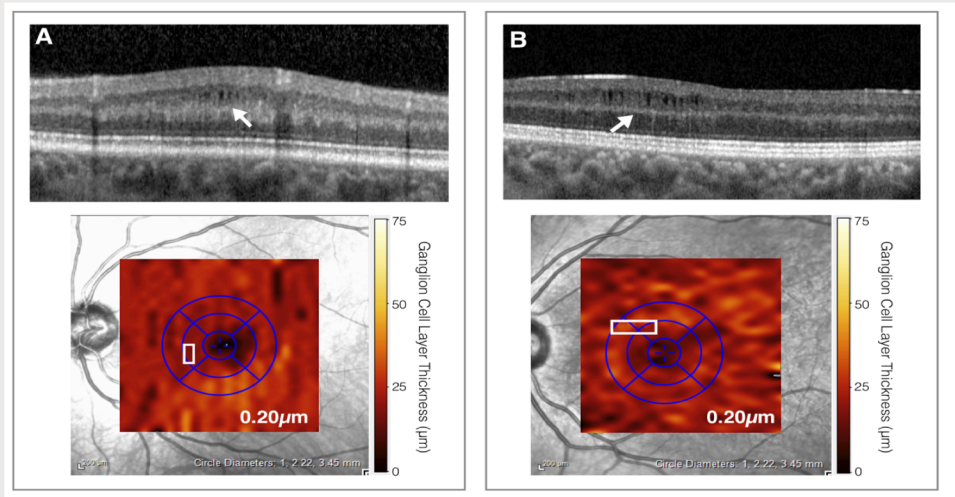


**Table 3: OCT results**

| | PPON cases | Controls |
|---|---|---|
| **Peripapillary ring scan** | | |
| **N (cases)** | 13 | 13 |
| **pRNFL µm, median (range)** | 60.5 (49 – 91) | 103 (94 – 112) |
| **Macular volume scan** | | |
| **N (cases)** | 12 | 13 |
| **GCIPL µm, median (range)** | 45 (35 – 72) | 88 (69 – 91) |
| **INL µm, median (range)** | 39 (34 – 51) | 37.5 (33 – 41) |
| **MMO, n (%)** | 6 (50%) | 0 (0%) |

**Conclusion** This cohort suggests that progressive visual failure in early multiple sclerosis predominantly affects males and is a bilateral disease associated with primary progressive multiple sclerosis.

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